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Fetal cavum septum pellucidum nomogram and its relationship with fetal Doppler: a prospective study of a Turkish population

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ABSTRACT

Aim: Septum pellucidum is a thin membrane with right and left leaves, and cavum septum pellucidum (CSP) is formed in the intermembrane region. This study investigates CSP nomogram dimensions for all trimesters in the Turkish population. In addition, the relationship between fetal Doppler flow and CSP size was investigated in this study.

Material and Method: This study was designed as a prospective cohort between 2019-2020. Pregnant women between 19-42 weeks who were followed up at University of Health Sciences Tepecik Training and Research Hospital, Department of Obstetrics and Gynecology were included in the study.

Results: A total of 517 fetuses meeting our criteria were included in this prospective study. In the second trimester (19-28 weeks) CSP width (4.12±0.88 vs. 4.91±1.42, p<0.001) and length (7.95±1.04 vs. 9.48±2.19, p<0.001) were significantly higher than in the third trimester (28-42 weeks). While the mean CSP width increased up to 32nd weeks, there was no clear increase-decrease pattern between 32nd-38th weeks, and it was observed to decrease after 38th weeks. The mean CSP length increased up to 29th weeks, while there was no clear increase-decrease pattern between 29th-38th weeks, but decreased after 38th weeks. While a significant correlation was observed between gestational week and CSP width (r=0.118, p=0.010), there was no significant correlation between CSP length (r=0.086, p=0.062). A significant correlation was observed between biparietal diameter (BPD) and CSP width (r=0.180, p<0.001) and length (r=0.202, p<0.001), but not with head circumference (HC). There was a significant correlation between middle cerebral artery (MCA) systolic/diastolic ratio (S/D) (r=0.185, p<0.001), pulsatility index (PI) (r=0.210, p<0.001) and resistive index (RI) (r=0.233, p<0.001) and CSP length, but not with CSP width.

Conclusion: Turkish population fetal CSP nomogram is presented in this study. Fetal middle cerebral artery Doppler measurements (S/D, PI, and RI) showing cerebral blood flow correlate with CSP length, but not with CSP width. There was no correlation between fetal umbilical artery Doppler measurements and CSP sizes. The results pave the way for population-based studies with much larger samples.

Keywords: Cavum septum pellucidum, nomogram, umblical artery, middle cerebral artery, Doppler

INTRODUCTION

In the anterior part of the brain, there are two midline cavities. These are the cavum septum pellucidum (CSP) and the cavum vergae (CV). These formations are cavities formed by the leaves of the midline septum pellucidum during brain morphogenesis. Septum pellucidum is a thin membrane with right and left leaves, and CSP is formed in the intermembrane region. The CV is the posterior extension of the CSP, associated with the CSP but lying behind the columns of the fornix (1). Various views of the embryogenesis of these cavities have been proposed. Although it is often suggested that they occur as a result of cavitation of the medial lower commissural plate (2), the exact mechanism of formation is not clear (3,4).

The septum pellucidum acts as an information transfer center: It transmits visceral information via the hypothalamic autonomic system to the hippocampus, amygdala, habenula, and reticular formation in the brainstem. Therefore, it is thought to play a role in functions such as mental process of self-care, competence, finding food, sexuality, attention and activity by playing a role in sleep-wake and emotional response to the environment.

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The axial transthalamic plane is the standard plane in which biparietal diameter and fetal head circumference are measured (5). The symmetry of the CSP, thalamus, and cerebral hemispheres can be evaluated in this section, and many midline malformations associated with the absence of CSP can also be detected in this section (6,7). In its absence, preliminary diagnoses of corpus callosum agenesis, holoprosencephaly, septo-optic dysplasia, and lissencephaly come to mind (4).

The cavum septum pellucidum is a very important structure in the evaluation of the fetal neural axis, which is an important component of fetal anatomy screening, and prenatal CSP evaluation is important for correct planning of postnatal follow-up of anomalies (4,8). Measurement dimensions can affect prognosis, although studies are often based on its presence and absence. For this reason, nomograms are tried to be created. Today, nomograms for CSP measurement are often considered in second trimester screening, but size change is important in all trimesters. Population-based variations can also occur, and population-based nomograms are primary tools for reflecting racial measurements (9). Therefore, in this study, it was planned to examine CSP sizes and size changes according to gestational weeks. This study investigates CSP nomogram dimensions for all trimesters in the Turkish population. In addition, the relationship between fetal Doppler flow and CSP size was investigated in this study.

MATERIAL AND METHOD

The study was carried out with the permission of İzmir Tepecik Training and Research Hospital Non-interventional Clinical Researches Ethics Committee (Date: 13.03.2019, Decision No: 2019/4-2). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Design

This study was designed as a prospective cohort between 2019-2020. Pregnant women between 19-42 weeks who were followed up at University of Health Sciences Tepecik Training and Research Hospital, Department of Obstetrics and Gynecology were included in the study. All participants were informed and informed voluntary consent was obtained.

Pregnant women using medication and those; with multiple pregnancies; with in vitro fertilization (IVF) pregnancies; with major or minor fetal anomalies; with known type 1 and type 2 diabetes mellitus; with gestational hypertension/preeclampsia; with fetal growth restriction; with hepatitis, gastroenteritis, pyelonephritis, or urolithiasis; and with incomplete records and/or whose records could not be reached were excluded from the study.

Ultrasound Examinations

Ultrasound assessment was performed (Toshiba AplioTM 500; Toshiba Medical Systems Inc., USA) equipped with an abdominal 3.5 MHz convex transducer. All measurements were performed by a single sonographer (B.B.) with the Doppler certificate of The Fetal Medicine Foundation in order to avoid differences. All examinations were performed in the supine position. First, biparietal diameter (BPD) and head circumference (HC) measurements of the fetus were taken. These measurements were made in the axial plane, with the calvarium symmetrical, in the plane of the thalamus and cavum septum pellucidum, and the cerebellum was not included in the image. BPD was measured in millimeters from outside to inside. The HC was measured in millimeters circumferentially from the outside edge of the calvarium. The probe was then rotated slightly to the cephalic part and the fluid-filled CSP was observed between the anterior horns of the lateral ventricles. The maximum anterior and posterior width between the inner boundaries of the CSP was measured in this plane as previously described by Jou et al. (10). Doppler measurements were made from both umbilical arteries and the middle 1/3 of the umbilical cord, and locations close to the fetus or placenta were avoided. In fetal middle cerebral artery (MCA) Doppler measurements, after determining the vascular structures of the Willis polygon with the help of color coding, measurements were made from the 1/3 beginning of the MCA near the origin from a. carotis interna. Traces in Doppler were followed until at least 3, at most 10 consecutive waves were obtained.

Statistical Analysis

Statistical Package for the Social Sciences version 26.0 (IBM Corporation, Armonk, New York, US) was used in the analysis of the data, and the significance level was taken as $p<.05$ in all analyses. Shapiro-Wilk test was used to determine the distribution of the data. Student's t-test was used for normally distributed data in comparison of the groups and the Mann-Whitney U test was used to compare the data that could not show normal distribution. Pearson's correlation coefficients analysis was performed to determine the relationship between parameters. For the number of samples, power analysis was performed with G-power 3.1.9.7 version. Accordingly, the minimum number of patients for each group was calculated as 33.

RESULTS

A total of 517 fetuses meeting our criteria were included in this prospective study. Demographic and clinical characteristics of the study participants are shown in **Table 1**. The mean age of the pregnant women was

28.1±5.7, and 236 (45.7%) were nulliparous and 281 (54.3%) were multiparous. The body mass index (BMI) was 28.4±4.8 kg/m² and 127 (24.5%) pregnant women were smoking. The mean CSP width was 4.77±1.37, and the CSP length was 9.21±2.11. (**Table 1**).

Table 1. Demographic and clinical characteristics of the study participants

	n=517
Maternal age (year) (mean±SD)	28.1±5.7
Parity (n,%)	
Nulliparous	236 (45.7%)
Multiparous	281 (54.3%)
BMI (kg/m²)	28.4±4.8
Smoking (n,%)	127 (24.5%)
CSP width (mm) (mean±SD)	4.77±1.37
CSP length (mm) (mean±SD)	9.21±2.11

Abbreviations: BMI: body mass index, CSP: cavum septum pellucidum, SD: standard deviation

The cavum septum pellucidum measurements according to trimesters were compared in **Table 2**. Accordingly, in the second trimester (19-28 weeks) CSP width (4.12±0.88 vs. 4.91±1.42, p<0.001) and length (7.95±1.04 vs. 9.48±2.19, p<0.001) were significantly higher than in the third trimester (28-42 weeks). (**Table 2**).

Table 2. Cavum septum pellucidum measurements according to trimesters

	Second Trimester (19-28 weeks) n=358	Third Trimester (28-42 weeks) n=159	p
CSP width (mm) (mean±SD)	4.12±0.88	4.91±1.42	<0.001
CSP length (mm) (mean±SD)	7.95±1.04	9.48±2.19	<0.001

Abbreviations: CSP: cavum septum pellucidum, SD: standard deviation

Mean width, length and standard deviation (SD) intervals according to gestational weeks were examined in **Table 3**. The mean CSP width ranged from 2.60 (19th week) to 5.80 (32nd week). The mean CSP length ranged from 7.30 (19th week) to 11.22 (29th week). The mean CSP width was between 2.06 (19th week) and 5.52 (32nd week) in -2 SD, and the mean CSP length was between 6.37 (19th week) and 10.42 (29th week) in -2 SD. The mean CSP width was between 3.13 (19th week) and 6.29 (35th week) in +2 SD, and the mean CSP length was between 8.22 (19th week) and 12.50 (33rd week) in +2 SD. (**Table 3**). While the mean CSP width increased up to 32nd weeks, there was no clear increase-decrease pattern between 32nd-38th weeks, and it was observed to decrease after 38th weeks. The mean CSP length increased up to 29th weeks, while there was no clear increase-decrease pattern between 29th-38th weeks, but decreased after 38th weeks (**Figure 1**).

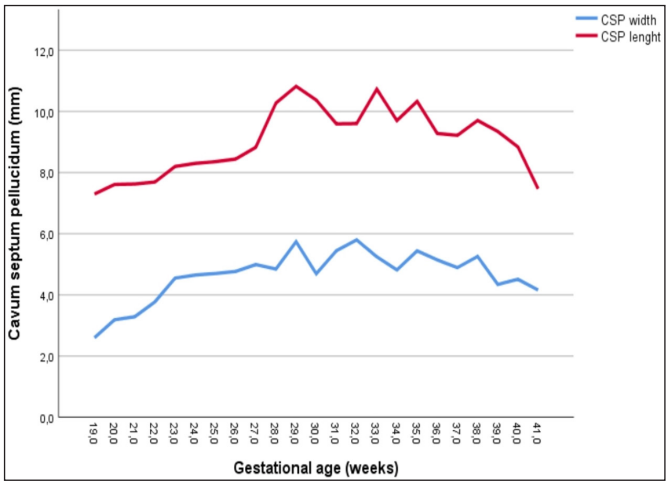

Figure 1. Distribution of cavum septum pellucidum measurements according to gestational weeks

Table 3. Mean width, length and standard deviation intervals by gestational weeks

Gestational age (weeks)	Number of cases	CSP width (mm) -2SD	Mean CSP width (mm)	CSP width (mm) +2SD	CSP length (mm) -2SD	Mean CSP width (mm)	CSP length (mm) +2SD
19	37	2.06	2.60	3.13	6.37	7.30	8.22
20	36	2.75	3.18	3.61	6.81	7.61	8.40
21	36	3.02	3.28	3.55	6.99	7.65	8.30
22	37	3.45	3.77	4.09	6.48	7.69	8.90
23	36	4.50	4.55	4.59	7.93	8.20	8.46
24	46	4.60	4.65	4.69	8.03	8.30	8.56
25	48	4.57	4.70	4.82	8.10	8.35	8.60
26	46	4.57	4.76	4.96	7.84	8.44	9.03
27	19	4.66	4.99	5.32	7.65	8.82	9.99
28	17	4.55	4.84	5.13	9.66	10.27	10.87
29	17	4.90	5.50	6.10	10.42	11.22	12.02
30	17	4.27	4.92	5.56	9.52	10.67	11.72
31	16	5.13	5.66	6.20	8.44	9.99	11.54
32	16	5.52	5.80	6.07	9.03	9.60	10.16
33	12	4.64	5.24	5.85	8.94	10.72	12.50
34	12	4.43	4.81	5.20	9.11	9.70	10.28
35	12	4.58	5.44	6.29	9.54	10.32	11.11
36	11	4.74	5.14	5.53	8.59	9.27	9.96
37	10	4.56	4.89	5.21	8.72	9.21	9.70
38	12	4.72	5.25	5.79	8.55	9.70	10.85
39	8	3.69	4.34	4.99	8.33	9.34	10.34
40	9	4.15	4.51	4.86	8.38	8.83	9.29
41	7	3.23	4.15	5.08	6.76	7.46	8.17

Abbreviations: CSP: cavum septum pellucidum, SD: standard deviation

The correlation between gestational age, fetal head biometry and fetal Doppler values and CSP width and length is shown in **Table 4**. While a significant correlation was observed between gestational week and CSP width (r=0.118, p=0.010), there was no significant correlation between CSP length (r=0.086, p=0.062). A significant correlation was observed between BPD and CSP width (r=0.180, p<0.001) and length (r=0.202, p<0.001), but not with HC. There was a significant correlation between

MCA systolic/diastolic ratio (S/D) (r=0.185, p<0.001), pulsatility index (PI) (r=0.210, p<0.001) and resistive index (RI) (r=0.233, p<0.001) and CSP lenght, but not with CSP width. (**Table 4**).

Table 4. The correlation between gestational age, fetal head biometry and fetal Doppler values and CSP width and length

	CSP width (mm)	CSP length (mm)
Gestational age (weeks)	r=0.118, p=0.010	r=0.086, p=0.062
BPD (mm)	r=0.180, p<0.001	r=0.202, p<0.001
HC (mm)	r=0.074, p=0.111	r=0.081, p=0.079
UA S/D	r=-0.012, p=0.802	r=-0.107, p=0.123
UA PI	r=-0.017, p=0.710	r=-0.082, p=0.077
UA RI	r=-0.022, p=0.635	r=-0.136, p=0.083
MCA S/D	r=0.064, p=0.198	r=0.185, p<0.001
MCA PI	r=0.025, p=0.583	r=0.210, p<0.001
MCA RI	r=0.062, p=0.183	r=0.233, p<0.001

Abbreviations: CSP: cavum septum pellucidum, BPD: biparietal diameter, HC: head circumference, UA S/D: umbilical arterial systolic/diastolic ratio, UA PI: umbilical arterial pulsatility index, UA RI: umbilical arterial resistive index, MCA S/D: middle cerebral arterial systolic/diastolic ratio, MCA PI: middle cerebral arterial pulsatility index, MCA RI: middle cerebral arterial resistive index

DISCUSSION

The septum pellucidum is a structure containing translucent glial cells, neurons, nerve fibers and veins that associated with the choroid plexus and extending from the lamina terminalis to the splenium of the corpus callosum (3,4). The potential cavity between the leaves of the septum pellucidum is called the cavum septum pellucidum. The embryological development of CSP is related to the embryological development of the septum pellucidum. The development of CSP begins at 10-12 weeks of gestation and reaches its adult form at 17th weeks of gestation, simultaneously with the corpus callosum. CSP can often be seen on transabdominal ultrasonography between 18-37 weeks or when the biparietal diameter is between 44-88 mm (6). Its absence is well known and associated with severe anomalies, and the preliminary diagnosis of corpus callosum agenesis, holoprosencephaly, septo-optic dysplasia and lissencephaly comes to mind (4). However, literature about its dimensions is limited. It has been suggested that the anatomical differences detected in the septum pellucidum may also reflect possible embryonic developmental disorders in the adjacent anatomical structures (11,12). Large CSP in adults is thought to be associated with mental disorders. In this context, patients with schizophrenia are the most studied psychiatric patient group, and it has been argued that the higher rates of "wide CSP" in patients with schizophrenia than healthy patients are an anatomical finding that supports the neurodevelopmental hypothesis proposed for the etiology of schizophrenia. The dimensions of the CSP may reflect the evolution of associated structures. Therefore, CSP development nomogram consisting of healthy fetuses is important. In this study, fetal CSP nomogram was planned in the Turkish population. To the best of our knowledge, this study is the study with the largest sample size investigating CSP nomogram dimensions for all trimesters in the Turkish population. In addition, for the first time in the literature, the correlation between fetal Doppler flow and CSP size was examined in this study.

Studies investigating the nomogram of all gestational weeks are limited in the literature. Falco et al. (13) examined the CSP width of 251 fetuses between 15 and 41 weeks in the Italian population in 2000. Overall, the average CSP widths were higher than our values. In their study, the mean CSP width was increasing by 31 weeks. On the other hand, we observed that CSP width increased until 32 weeks, and CSP length increased until 29 weeks. Tao et al. (14) studied CSP width in a total of 322 fetuses between 25 and 39 weeks in the Chinese population in 2013. In their study, the mean CSP width between the respective weeks was generally higher than in our study. CSP values at all gestational weeks were very close to each other, the range was very narrow, and no significant correlation was observed between CSP values and gestational weeks. On the other hand, we observed a significant correlation with the gestational week. Zhao et al. (15) examined 260 fetuses between 18-36 weeks in the Chinese population in 2019. In their study, CSP width and length increased up to 25 weeks. Similar to our study, CSP width was correlated with gestational week and BPD. We observed that CSP width increased until 32 weeks, and CSP length increased until 29 weeks. Ho et al. (16) investigated 503 fetuses between 15 and 39 weeks in the American population in 2020. Most of these measurements were made at 18 to 20 weeks at the time of the anatomy scan. CSP width was correlated with gestational week, similar to our study. However, only 1 fetus was examined at 38 and 39 weeks in this study, whereas we investigated 12 and 8 fetuses at 38 and 39 weeks, respectively. Yakubu et al. (17) examined the CSP width of 228 fetuses between 14-40 weeks in the Nigerian population in 2021. The mean CSP width was particularly high in the later weeks (36 weeks: 7.11±0.81, 37 weeks: 7.11±0.81, 38 weeks: 7.11±0.81, 39 weeks: 7.11±0.81 and 40 weeks: 9.30±0.28). However, they were able to examine only 4 fetuses at 39 weeks and only 2 fetuses at 40 weeks, whereas we investigated 8, 9 and 7 fetuses at 39, 40 and 41 weeks, respectively. In their study, CSP width was correlated with gestational week, similar to our study. We observed that CSP width increased until 32 weeks, and CSP length increased until 29 weeks.

As far as we know, there are only two studies investigating the measurement of CSP in the Turkish population. However, these studies had several limitations.

Serhatlioglu et al. (18) studied CSP sizes on 130 fetuses in 2003. This study included samples between 16-38 weeks. Accordingly, in the second and third trimesters, they found the mean CSP width to be 3.1±1.5 and 5.0±1.4, respectively, and the CSP length to be 7.7±2.6 and 11.7±2.5, respectively. In our study, second trimester and third trimester CSP widths were 4.12±0.88 and 4.91±1.42, respectively, and CSP length was 7.95±1.04 and 9.48±2.19, respectively. The difference in CSP according to trimesters was significant similar to our study. In the same study, they observed a correlation between gestational weeks, BPD and CSP width-length. We observed a significant correlation between BPD and CSP width and length, and between gestational week and CSP width. We did not observe correlation between gestational week and CSP length. The fact that our sample number was much higher may have caused this result. Again, they could not provide mean and standart deviation values in their studies, probably because the sample numbers were small. In addition, the correlation between fetal Doppler and CSP was not investigated in their studies. Arisoy et al. (19) retrospectively analyzed the nomogram of CSP width between 15-28 weeks in 2022. This study does not examine all gestational weeks, the nomogram is limited to the second trimester only. They found the second trimester mean CSP width to be 4.1±0.8. Our second trimester mean CSP width is 4.12±0.88, which is very close to this value. CSP width was correlated with gestational week and BPD, similar to our study. In their study, the 95th percentile values of CSP width between 15-28 weeks of gestation were found to be 3.7-7 mm. In our study, the +2SD CSP values were 3.13-5.13.

For the first time in the literature, we investigated the relationship between fetal Doppler values and CSP dimensions. We did not observe a significant correlation with fetal umblical artery Doppler measurements. However, fetal middle cerebral artery Doppler measurements (S/D, PI and RI) showing cerebral blood flow were correlated with CSP length, but not CSP width. In fact, the fetal cerebral artery is the main artery supplying the brain. The umbilical artery is not directly related to the brain. This may reflect the results. However, randomized controlled studies are needed on this subject.

This study had some limitations. Although it was higher than the literature, our sample number at the later gestational week was still limited. This study had also had strengths. For the first time in the literature, we investigated the relationship between fetal Doppler values and CSP dimensions. Also, to the best of our knowledge, this is the largest Turkish fetal CSP population study that includes all weeks of gestation.

CONCLUSION

Turkish population fetal CSP nomogram is presented in this study. Fetal CSP width increases up to 32 weeks of gestation and fetal CSP length increases up to 29 weeks. Third trimester CSP measurements are significantly higher than second trimester CSP measurements, which may be related to the growth of fetal head biometry. Fetal middle cerebral artery Doppler measurements (S/D, PI, and RI) showing cerebral blood flow correlate with CSP length, but not with CSP width. There is no correlation between umbilical artery values and CSP measurements. Population-based studies with much larger samples are required to establish clear values about fetal CSP measurements.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of İzmir Tepecik Training and Research Hospital Non-interventional Clinical Researches Ethics Committee (Date: 13.03.2019, Decision No: 2019/4-2).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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